

HEALTH HAZARD EVALUATION REPORT

HETA 91-178-2220
GEISINGER WYOMING
VALLEY MEDICAL CENTER
WILKES BARRE, PENNSYLVANIA

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 29(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer and authorized authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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NIOSH

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I. SUMMARY

A management request was received from the Director of Diagnostic Services of Geisinger Wyoming Valley Medical Center (GWVMC) in Wilkes Barre, Pennsylvania, for a Health Hazard Evaluation of the effectiveness of procedures used at the hospital to control exposures of health care workers to aerosolized ribavirin (AR). No health symptoms from AR were indicated on the request.

Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic nucleoside analogue which is used for the short-term treatment of respiratory syncytial virus (RSV) infection. Occupational exposure criteria have not been established for ribavirin. Because the drug has been reported to be teratogenic and/or embryo-lethal in several animal species, there is concern about its potential reproductive effects in humans.

Personal breathing zone sampling and area air sampling for AR were conducted over a 16-hour administration to a 5-month old infant. Twelve-inch cubical "Care Cube" delivery hoods and Small Particle Aerosol Generators (SPAG-2®) were used for administration of AR. The hospital had recently installed a plastic enclosure to contain the ribavirin aerosol in the administration area. Additionally, health care workers and visitors were required by hospital policy to wear supplied-air hood respirators when inside the plastic-enclosed administration area.

Ribavirin concentrations in short-term breathing zone samples ranged from 125 to 670 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$), while simultaneously-collected samples from the inside of the supplied-air respirator had no detectable ribavirin (limit of detection: 2 $\mu\text{g}/\text{sample}$). Full-shift personal samples (cassettes inside the respirator hoods when in administration area) had no detectable ribavirin. While area samples collected inside the enclosure had notable ribavirin concentrations (7.4 and 12.4 $\mu\text{g}/\text{m}^3$), samples collected outside the enclosure had no detectable ribavirin. Nurses and respiratory therapists donned the hoods without apparent difficulty. The hoods did not interfere with their work.

The sampling results from this Health Hazard Evaluation suggest that exhausted plastic enclosures, maintained under negative pressure, are capable of controlling the spread of ribavirin aerosol to adjacent areas. Supplied-air respirators were a feasible method of control for aerosolized ribavirin and were accepted by health care workers. Control of exposure at the source, by engineering methods and work practices, is preferable to reliance on respirators. Recommendations addressing training and certain aspects of the respirator program can be found in Section VIII (pages 15-18) of this report.

KEYWORDS: SIC 8062 (General Medical and Surgical Hospitals), CAS number 36791-04-5, ribavirin, Virazole®, 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboximide, aerosolized drugs, aerosolized pharmaceuticals, health care workers, teratogen, respirators, aerosol containment system.

II. INTRODUCTION

A management request was received from the Director of Diagnostic Services of Geisinger Wyoming Valley Medical Center (GWVMC) in Wilkes Barre, Pennsylvania, to evaluate the effectiveness of procedures used at the hospital to control exposures of health care workers (HCWs) to aerosolized ribavirin (AR). GWVMC is licensed for approximately 230 beds and employs approximately 900 employees. No health symptoms attributed to AR were indicated on the request.

Much of the concern about occupational exposure to pharmaceutical aerosols has centered around the use of AR. The reports of adverse reproductive effects of ribavirin exposure in animal studies have raised concerns among HCWs who administer ribavirin; many of these workers are in their reproductive years. Occupational exposure criteria for AR have not been established by the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), or the Occupational Safety and Health Administration (OSHA).

Variables that can affect HCWs' exposure to AR include the method of administration, use of scavenging devices, and implementation of certain work practices, such as turning off the aerosol generator before opening the administration device. Other factors that may affect exposure include the concentration of AR produced by the aerosol generator and room ventilation rates.

GWVMC had implemented new policies and procedures regarding ribavirin administration in 1991. As part of the new procedures, a plastic enclosure was installed to contain ribavirin aerosol in the administration area. Additionally, HCWs and visitors were required by hospital policy to wear supplied-air hood respirators when entering the plastic-enclosed administration area.

A NIOSH industrial hygiene survey was conducted on January 24-25, 1992. Air sampling for AR was conducted, room ventilation rates were measured, engineering controls were evaluated, and the respiratory protection policy and equipment were reviewed.

III. BACKGROUND

A. *Aerosolized Drugs*

The administration of pharmaceutical aerosols, such as AR, is rapidly expanding in medicine. Asthma, chronic obstructive pulmonary disease, and pulmonary infections are frequently treated with aerosols of sympathomimetics, beta-agonists, corticosteroids, and antimicrobials. The advantages to the patient include rapid onset of therapeutic action, optimized delivery of the drug to the site of action, and reduction in unwanted systemic side-effects. However, aerosol delivery results in increased exposure to the HCW, compared with other administration routes. The difficulty in controlling the spread of aerosols, along with their small particle size, contributes to the risk of occupational exposure.

B. *Uses of Ribavirin*

Ribavirin is a synthetic nucleoside that is licensed by the U.S. Food and Drug Administration (FDA) for the short-term treatment of severe respiratory syncytial virus (RSV) infections.¹ Its antiviral activity is thought to result from inhibition of RNA and DNA synthesis, which subsequently inhibits protein synthesis and viral replication.² Aerosolized ribavirin has also been used to treat both influenza B pneumonia and RSV pneumonia in immunocompromised adults.^{3,4,5,6}

C. *Preparation and Administration*

Ribavirin is commercially available as a sterile, lyophilized powder, which is initially reconstituted by adding 50-100 milliliters (mL) additive-free sterile water to a 6 gram vial. The initial solution is transferred to a sterile wide-mouthed flask, which serves as the reservoir for the aerosol generator and is further diluted to a final volume of 300 mL with sterile water.

Ribavirin aerosol is generated by a Small Particle Aerosol Generator (Model SPAG-2® nebulizer) marketed by the drug manufacturer. The SPAG-2® nebulizer delivers AR at a rate of approximately 14 liters per minute (L/min). When the recommended starting solution of 20 milligrams of ribavirin per milliliter (mg/mL) of sterile water is used, the average concentration of aerosol generated by the unit is expected to be 190 milligrams per cubic meter (mg/m³), according to the manufacturer.⁷ The small particle size (1.0-1.3 micrometer mass median diameter) of the ribavirin aerosol permits deep penetration of the drug into the patient's lungs.⁸

The aerosol can be delivered to the patient by a variety of methods, including face mask, head hood (i.e., Aerosol Delivery Hood®), croup or mist tent, oxygen hood, or direct coupling to tracheostomy. At GWVMC, ribavirin was administered in twelve-inch cubical "Care Cube" disposable hoods.

Respiratory therapists set-up and dismantled the ribavirin delivery system. This entailed transferring the liquid ribavirin solution to the SPAG-2® unit's reservoir, securing the reservoir in the unit, turning on the unit, checking/adjusting the airflow settings to the manufacturer's specifications, and ensuring that the delivery equipment was secure and functioning properly. AR was delivered from the SPAG-2® to the Aerosol Delivery Hood® (ADH®) or tent through flexible tubing. The child was then placed into the administration device after the aerosol flow was started.

Every three to five hours, the respiratory therapists (RTs) checked the patient's vital signs, the solution volume, and function of the nebulizer. Bronchodilator medications were also administered at this time, if ordered by the attending physician. The RTs spent about 15 to 45 minutes inside the enclosure during each visit. The remainder of the time was spent with other patients throughout the hospital.

D. Hospital Policies and Procedures

To address the concerns of hospital management and of respiratory therapists, and nurses who administer AR, new policy and procedures were implemented in October 1991, in an attempt to limit occupational exposures to AR. The GWVMC procedures for ribavirin administration consists of the following procedures (adapted from the hospital's procedure manual):

ADMINISTRATION:

- The drug will be administered as 16-hour therapy for 3-5 days.
- Persons who are currently pregnant will be excluded from entering the treatment room during therapy.
- Persons who are medically unable to wear a respirator will be excluded from entering the treatment room during therapy.
- The drug will be administered via a Small Particle Aerosol Generator (SPAG®) into an oxygen cube placed within the administering area.

ROOM SET UP:

- The administering area will be exhausted through a high efficiency particulate air (HEPA) filtration system.
- The room will be under negative pressure relative to adjacent areas.
- Polyvinyl curtains will separate the administration area from the clean area.
- Warning signs will be posted at all access points to the administration area.
- All materials and equipment required for administration of ribavirin will be maintained on a cart outside the administering area for easy use.

WORK PRACTICES/PERSONAL PROTECTIVE EQUIPMENT

ALL STAFF:

- The SPAG® aerosol generator must be turned off 10 minutes prior to:
 - (1) each time the [administration] cube is opened or child accessed, and
 - (2) when the filters on the HEPA filtration unit are being changed.
- Any equipment used in the room must be wiped down with a damp cloth prior to leaving the room.
- Personal protective equipment required by everyone entering the administration area includes the following:
 - i. Full body covering (including head and foot) of disposable clothing to be donned prior to entry into the administration area and removed and placed in appropriate disposal receptacles upon exiting the room,
 - ii. Eye protection (goggles) is recommended for persons who notice eye irritation upon exposure to ribavirin,
 - iii. Surgical masks are required for those persons who are not required to wear respiratory protection as defined below, and
 - iv. Respiratory protection is required for all persons in the administration area.

NURSING:

- Post warning signs.
- Conduct daily evaluations of room pressure using smoke pencils.

- All trash cans and linen hampers will be placed in the clean area for environmental services pick-up.
- The patient's medical record should not be brought into the room. Nursing documentation forms can be left in the room, but should be placed in a drawer or otherwise protected from ribavirin deposition.
- Prior to removing the patient from the administration area, he/she must be bathed to remove deposited ribavirin.
- If a respirator is worn, the user is responsible for the daily cleaning and care of the respirator.

RESPIRATORY THERAPY:

- Respiratory therapy is responsible for setting up and monitoring the administration of ribavirin.
- The filter in the HEPA exhaust unit will be changed by respiratory therapy as indicated by the exhaust unit.
- If a respirator is worn, the user is responsible for the daily cleaning and care of the respirator.

ENVIRONMENTAL SERVICES:

- Flat surfaces within the treatment room will be washed once a day.
- Waste will be collected from the room as often as necessary to eliminate accumulation of disposable materials.
- A terminal cleaning of all surfaces of the room and all surfaces of the control hood, air filtration unit, and stretcher must be conducted after drug administration is complete.
- The soiled linen hampers shall consist of plastic bags lined with mesh bags.
- The soiled linens will be carried down to laundry collection.

A polyvinyl curtain was used to block-off a portion of the patient room. The curtain extended from the floor to the ceiling and had no gaps, except for an entry area kept closed with magnets. The enclosed area was approximately 9 X 8 X 7.5 feet (540 cubic feet (ft³)). Excluding the entry and bathroom, the patient room was 15 X 11 X 7.5 feet (1238 ft³). A HEPA filtration system (Control Resource Systems, Model 600H - K0021DO, Michigan City, Indiana) was installed to filter AR from the enclosed administration area. Air was exhausted into a ceiling duct, drawn through the HEPA filter, and exhausted to the outside of the building. The curtain-enclosed area did not have a supply diffuser. The bathroom had an exhaust, and there was a supply diffuser located outside the enclosure.

During our visit, a five-month old was administered AR in a 1 X 1 X 1 foot "Care Cube" for 16 hours. The administration was conducted inside the curtain enclosure. The SPAG generator was not turned off before employees entered the enclosure.

Employees and visitors who entered the enclosure wore NIOSH/MSHA (Mine Safety and Health Administration)-approved Willson Air Supplied Hood® respirators (Model 4000, Type C, NIOSH/MSHA approval number: TC-19C-166), manufactured from DuPont Tyvek®. The respirators were connected to the hospital's breathing air supply. Airflow was set with a Precision® medical rotameter at 45 liters per minute (L/min) (rotameter range: 10-70 L/min). Latex exam gloves and gowns were worn inside the enclosure. Shoe covers were not used.

IV. EVALUATION CRITERIA

A. *Toxicology of Ribavirin*

In animal studies, ribavirin has been shown to be teratogenic and embryolethal in rats, mice, and hamsters, and embryolethal in rabbits.^{9,10,11,12} One study of a small number of baboons did not show teratogenic effects.¹³ However, a NIOSH review of this study concluded that the study did not provide adequate evidence to evaluate reproductive outcome due to a small number of test animals. Three studies in rats showed degenerative or histopathologic testicular effects. Eight other studies in rats, mice, dogs, and monkeys induced no testicular effects.¹⁴ Ribavirin was found to be toxic to lactating animals and their offspring.¹⁵

The adverse reproductive effects seen in animal studies have raised concerns among HCWs who administer ribavirin; many of these workers are in their reproductive years. Ribavirin has not been linked to fetal abnormalities in humans; however, given the wide spectrum of teratogenic potential in several animal species, avoidance of ribavirin prior to pregnancy, during pregnancy, and during lactation has been recommended.¹⁶ At present, the potential reproductive health effects of occupational exposure to ribavirin are unknown.

Adverse effects occur infrequently in patients receiving AR; the more commonly-reported effects include respiratory and cardiovascular disturbances, rash, and skin irritation.^{16,17} Hemolytic anemia and suppression of erythropoiesis can occur when the drug is given orally or parenterally.^{16,18}

Acute effects due to environmental exposure to ribavirin aerosol include rhinitis and headache.^{16,18} The drug has been reported to precipitate on contact lenses, and eye irritation has been reported in employees wearing contact lenses.^{16,19}

B. *Pharmacokinetics of Ribavirin*

Following inhalation, ribavirin is deposited in the respiratory tract. It is then redistributed from the respiratory tract into the circulation with eventual

accumulation in erythrocytes. The extent of accumulation following inhalation has not been established, but following oral administration of a single dose of ribavirin, plasma and erythrocyte levels initially increased in parallel. Within two hours after administration, the plasma levels began to fall while erythrocyte levels continued to rise. Erythrocyte levels rose to a plateau at about four days and then declined with an apparent half-life of 40 days.²⁰

Ribavirin is believed to be metabolized in the liver. The major route of elimination of ribavirin and its metabolites appears to be renal. In healthy adults with normal renal function, excretion of ribavirin administered orally indicates that approximately 53% of a single dose is excreted within 72-80 hours.¹⁶ An additional 15% is excreted in the feces.¹⁶ No data are available regarding cutaneous or mucocutaneous absorption.

C. *Evaluation Criteria - Ribavirin*

No occupational exposure standard for ribavirin has been recommended by NIOSH, OSHA, or the ACGIH. The California Department of Health Services has suggested that an occupational exposure limit, based on a risk assessment model, can be calculated by applying a safety factor of 1000 to the no observed effect level (NOEL) in the most sensitive animal species.^{21,22} Using the model, a limit of $2.7 \mu\text{g}/\text{m}^3$ as an eight-hour time-weighted average (TWA) has been proposed. This calculation was based on a minute ventilation of 19 liters, an employee weight of 58 kilograms, and a pulmonary ribavirin retention rate of 70%. The model was based on pharmacokinetic data collected after administration of therapeutic doses, which may not be a reliable indicator of low-dose occupational exposure.

Although NIOSH has not issued an official policy statement on this subject, there is concern that the existing animal data may be inadequate to establish a NOEL. In view of the uncertainty about the health effects of ribavirin, it would be prudent to minimize exposures whenever possible to minimize the potential risks to HCWs.

D. *Evaluation Criteria - Ventilation*

The American Institute of Architects (AIA) Committee on Architecture for Health has published ventilation recommendations for hospitals. Isolation rooms are recommended to have a minimum of six total air changes per hour (ACH) and should be under negative pressure. Regular patient rooms are required to have a minimum of two total ACH.²³ These guidelines do not address the use of aerosolized pharmaceuticals.

V. METHODS

A. *Air Sampling Methodology and Laboratory Analysis*

1. Participants and Sample Types

Personal samples were collected in the workers' breathing zone. When the nurses entered the plastic enclosure, the filter cassettes were inside the air-supply hoods worn by the nurses. Two full-shift personal samples were collected from nurses, who provided care continually throughout their shift. Short-term samples, simultaneously collected inside the respirator hood and from the lapel, were obtained from two nurses, one respiratory therapist (RT), and the child's mother, while they were present in the enclosed administration area. A total of six full-shift area samples were collected: two samples inside the plastic curtain enclosure, two outside the enclosure (within the room), one outside the door, and one at the nurses station. Three 5-minute samples were collected from the interior of the "Care Cube" administration hood.

2. Sampling Methodology

Air sampling for AR was conducted according to NIOSH method 5027, utilizing 37-millimeter (mm) diameter, 1.0 micrometer (μm) glass fiber filters (type A/E, #61652, Gelman Sciences Inc., Ann Arbor, Michigan) in closed-face cassettes.²⁴ Each cassette was connected by flexible tubing to a battery-operated air sampling pump operated at a flow rate of 2.0 L/min for short-term personal and full-shift area samples. Full-shift personal sampling was conducted at 1.0 L/min to reduce the amount of noise produced by the sampling pump. Filter cassettes were placed inside the supplied-air hood before the nurses entered the enclosure. A flow rate of 1.0 L/min was utilized for 5-minute samples collected inside the "Care Cube" hood.

3. Laboratory Analysis

The glass fiber filters containing ribavirin were extracted with 3 mL sulfuric acid solution (pH = 2.5) in an ultrasonic bath and analyzed by high performance liquid chromatography (HPLC) using a cation exchange resin column. The HPLC was equipped with an ultraviolet detector set at 210 nanometers wavelength. The limit of detection (LOD) and limit of quantitation (LOQ) were 2 and 4.7 $\mu\text{g}/\text{sample}$, respectively.

D. *Ventilation Evaluation*

To determine if ribavirin could potentially migrate out of the treatment rooms, smoke tubes were used to visualize the direction of airflow around the enclosure and between the treatment room and the adjacent hallway.

Room ventilation and the HEPA-filtered exhaust (in the enclosure) airflow rates were measured using a Shortridge Instruments Air Data Flow Meter, CFM-88, Series 8405 (Shortridge Instruments, Scottsdale, Arizona). Three sets of measurements were made during the evaluation. Measurements were recorded with the front door closed and the bathroom door open (these were the usual positions).

VI. RESULTS AND DISCUSSION

A. *Air Sampling Results*

The two full-shift personal samples collected from nurses had no detectable ribavirin (limits of detection (LODs) were 5.4 and 5.5 $\mu\text{g}/\text{m}^3$ - see Table 1). Short-term lapel concentrations ranged from 125 to 670 $\mu\text{g}/\text{m}^3$. None of the simultaneously-collected, short-term, inside-hood samples had detectable ribavirin (see Table 2), but the limits of detection were relatively high (83 and 59 $\mu\text{g}/\text{m}^3$ for 12- and 17-minute samples, respectively).

Area samples collected inside the curtain enclosure had notable concentrations of ribavirin (7.4 and 12.5 $\mu\text{g}/\text{m}^3$); whereas, none of the samples collected outside the curtains had detectable ribavirin (LODs were 1.6 $\mu\text{g}/\text{m}^3$ - see Table 3). The results of area sampling are presented as full-shift TWA concentrations. The short-term personal concentrations (noted above) were collected only while the employee was inside the enclosure. Since the SPAG was not turned off while the HCW provided care to the infant (contrary to the hospital's written policy), higher short-term concentrations occurred.

Concentrations inside the "Care Cube" ranged from 86 to 90 micrograms per liter ($\mu\text{g}/\text{L}$). These values are below the manufacturer's recommended administration concentration of 190 $\mu\text{g}/\text{L}$, but may have been biased by the short sample time and location of the cassette inside the "Care Cube." However, changes in nebulizer flow rate also can dramatically affect the concentration of ribavirin aerosol.⁸ With a drying airflow maintained at 8 L/min, a nebulizer flow rate of 6 L/min results in a concentration of approximately 80-90 $\mu\text{g}/\text{L}$; however, a flow rate of 7 L/min results in a concentration of approximately 190 $\mu\text{g}/\text{L}$.⁸ The hospital reportedly used a nebulizer flow rate of 6 L/min, which would explain inside-cube concentrations between 80 and 90 $\mu\text{g}/\text{m}^3$. The usage of ribavirin solution by the SPAG was within the normal range specified by the manufacturer.

B. *Room Ventilation Measurements*

The airflow rate (mean of three measurements) exhausting the curtained enclosure was 259 cubic feet per minute (cfm). There were no air supply diffusers inside the enclosure. Based on a calculated curtained-enclosure volume of 540 cubic feet (ft^3), air changes per hour (ACH) for the enclosure

were calculated by dividing the amount of air exhausted per hour by the room volume. Assuming perfect mixing, the enclosure provides 29 ACH. The American Institute of Architects for hospital isolation rooms recommends a minimum of 6 ACH, but this recommendation was not specifically intended for enclosures within rooms.

The room's supply diffuser (located outside the enclosure) was not functioning. The bathroom exhaust (mean of 3 measurements) was 165 cfm. Based on the combined bathroom exhaust and HEPA-filtered exhaust, the calculated ACH for the entire room is 15.5 ACH.

Smoke tube tests indicated that the enclosure area was under negative pressure (air movement into the enclosure) with respect to the rest of the room. Smoke tests at the cracked doorway indicated that the entire room was under negative pressure with respect to the hallway.

C. Observations related to Supplied-Air Hood Respirators

The source of breathing air for the Willson supplied-air respirators (Model 4000) was the hospital's breathing air supply. According to hospital management, the air quality reportedly conformed to the American National Standards Institute/Compressed Gas Association (ANSI/CGA) G7.1-1989 Grade D requirements.²⁵ The manufacturer-supplied tubing was extended by the hospital with narrow Tygon® tubing. This tubing was susceptible to kinking. Airflow into the respirators was continuous flow, set at 45 L/min, as measured by a rotameter located at the air supply valve. The air supply valve was located outside the enclosure.

Air line respirators, as described in 30 CFR 11, Subpart J, use compressed air from a stationary source delivered through a hose under pressure. A number of specifications for supplied-air respirators can be found in the regulations. 30 CFR 11 specifies that the pressure shall not exceed 125 pounds per square inch (psi) at the point where the hose attaches to the air supply. A manufacturer submitting an airline respirator for certification must specify the operating pressure (8-40 psi for the Willson 4000) and the hose length, from 25 to 300 feet. At the lowest pressure and longest hose length, the device must deliver at least 170 L/min to the hood. At the highest pressure and shortest hose length, the flow rate must not exceed 425 L/min. Supplied-air respirators equipped with a hood and operated in a continuous flow mode have an assigned protection factor of 25 (see Appendix A and Table A-1 for an explanation of assigned protection factors).

The changes to the air tubing and the use of substandard airflow rates invalidate the NIOSH/MSHA approval. The usage of the respirator in this manner appears inconsistent with OSHA regulations (30 CFR 11 and 29 CFR 1910.134).

VII. CONCLUSIONS

The curtain-enclosure containment method used by GVWMC is an effective method to prevent the spread of AR and reduce exposures among hospital staff. Supplied-air respirators, when used as specified by the manufacture, will reduce exposures to AR. Supplied-air respirators (utilizing a loose-fitting hood) can be expected to provide a greater level of protection than disposable dust/mist/fume half-mask respirators, since they have a higher assigned protection factor (25 versus 5 or 10 for disposable half-mask respirators).²⁶ Based on observations during this survey, the use of supplied-air respirators is feasible for this application in a hospital environment.

VIII. RECOMMENDATIONS

The hospital management has implemented innovative and effective engineering controls to reduce the spread of aerosolized ribavirin (AR). In view of the uncertainties surrounding occupational exposure to ribavirin, hospital management determined that higher levels of respiratory protection (supplied-air respirators versus disposable particulate respirators) were required to adequately protect their employees. Since supplied-air respirators are capable of reducing contaminant exposures 2-½ to 5 times more than single-use respirators or air-purifying half-mask respirators, the implementation of supplied-air respirators by this hospital is consistent with the goal of minimizing occupational exposures.

Engineering controls (i.e., local exhausted enclosures), work practices, and administrative measures are preferable methods for control of exposures to airborne contaminants. NIOSH routinely makes recommendations regarding the use of respirators for workers exposed to workplace environments that contain hazardous concentrations of airborne contaminants. Such recommendations are made only when engineering controls are not technically feasible, while controls are being installed or repaired, or when emergency and other temporary situations arise.

The following recommendations are offered to ensure that ribavirin exposures are minimized among HCWs and other individuals who may enter areas where ribavirin is administered.

1. The hospital should make modifications to the supplied-air respirator hood so that it complies with NIOSH/MSHA-approval specifications (such as flow rate, operating pressures, and hose type).
 - ☞ Only the manufacturer's air hose, made specifically for the respirator, should be used.
 - ☞ The airflow to the supplied-air respirator hood should be increased to a minimum of 170 L/min. If this flow rate cannot be attained with the hospital's air supply, stationary compressed air cylinders may be used as an alternative source of breathing air. The manufacturer's specified air pressure, in conjunction with the recommended airflow rate, should be used when operating the respirator.
 - ☞ GWVMC should ensure that the breathing air for the respirator meets the requirements of the specification for Grade D breathing air as described in Compressed Gas Association Commodity Specification ANSI/GCA G-7.1-1989. In many cases, breathing air used in hospitals meets the *United States Pharmacopeia/National Formulary* (USP/NF) requirements for Grade N air (Air, U.S.P.), which are more stringent than the purity requirements for Grade D air.²⁵

An alternative to the supplied-air respirator is the powered-air purifying respirator (PAPR). The PAPR does not require a compressed air source.

This type of respirator is also available with loose-fitting hoods, but the breathing air is supplied from a portable, battery-operated air pump equipped with particulate filters. Like the loose-fitting supplied-air respirator, the PAPR also has an assigned protection factor of 25. The costs associated with using PAPRs may be less than that of making modifications to the supplied-air system.

2. Hospital management should note that all respirator use should take place within the context of a respiratory protection program. Elements of a minimally acceptable program are outlined in the OSHA respiratory protection standard (29 CFR 1910.134). Many of these elements have already been implemented by the hospital.
3. During the NIOSH visit, there was some discussion regarding proper methods of cleaning and disinfecting respirators. Cleaner and sanitizer solutions (for respirators) that clean effectively and contain a bactericide are commercially available. The bactericide is generally a quaternary ammonium compound, which has some disadvantages because its concentration must be adjusted to the composition of the local water to provide a constant degree of disinfection. Also, there is a possibility of dermatitis if the quaternary ammonium salts are not completely rinsed from the respirator.²⁷

An alternative is to wash the respirators in detergent, followed by a disinfecting rinse. Reliable effective disinfectants may be made from readily available household solutions, as follows:²⁷

☞ Hypochlorite solution (50 parts per million (ppm) chlorine) made by adding approximately 2 mL of hypochlorite (laundry) bleach to 1 liter of water. A 2-minute immersion disinfects the respirators.

☞ Aqueous solution of iodine (50 ppm iodine) made by adding approximately 0.1 mL tincture of iodine per liter of water. The iodine is approximately 7% ammonium and potassium iodide, 45% alcohol, and 48% water. Again, a 2-minute immersion is sufficient. Iodine may discolor the hoods.

The cleaned and disinfected respirators should be rinsed thoroughly with clean water to remove all traces of detergent and disinfectant. This is important to prevent dermatitis.²⁷

4. Training programs should be developed to educate HCWs about potential risks of ribavirin exposure. Education should not be limited to direct care personnel, but should include ancillary personnel such as phlebotomists, housekeepers, maintenance staff, and others who enter the room during treatment or must clean contaminated rooms, waste, and bedding. The staff should be educated to recognize situations that could result in increased occupational exposure. Pregnant or lactating HCWs, and HCWs

who are not actively avoiding pregnancy should be counseled about risk reduction strategies, such as alternate job assignments. Family members and visitors should be notified of potential health effects to ribavirin.

5. Various ribavirin administration and scavenging systems result in different levels of environmental contamination. All administration systems should include a mechanism to reduce environmental exposures to ribavirin. Administration and scavenging equipment should be maintained and visually inspected by the staff on a regular basis.
6. Rooms or enclosures where ribavirin is administered should conform to the American Institute of Architects recommendations for isolation rooms.²⁹ Rooms should provide a minimum of six total air changes per hour, and should be under negative pressure. Room air should be exhausted to the outside rather than recirculated to other areas of the hospital.
7. Air pressure in the ribavirin treatment room and enclosure should be evaluated before therapy begins, and daily thereafter. Ideally, ribavirin treatment should begin only if room air pressure is negative with respect to the hallway. This can be accomplished by observing the direction of airflow at the doorway with smoke tubes or by holding a piece of tissue paper at the cracked doorway.
8. The current GWVMC written policy of turning off the aerosol generator 10 minutes prior to opening the administration cube or accessing the child should be practiced by the staff when not contraindicated by the need for emergency access. This procedure could be accomplished by placement of a remote switch outside the room or use of a timer.
9. During aerosol therapy, ribavirin precipitate may be deposited on the patient and on the surrounding area. Care should be taken when ribavirin-contaminated clothing, bedding, or equipment is handled to prevent the dust from becoming airborne. Although dermal absorption is not thought to be significant, dermal exposure should be avoided to prevent unintentional oral ingestion or ocular contact. The use of personal protective equipment, including gloves, gowns, and goggles should be continued. The hospital's policy of cleaning surfaces and equipment in the treatment room should be continued.
10. In order to help reduce exposure of HCWs to ribavirin, medically unnecessary use of it should be avoided. Accordingly, medical staff should remain mindful of the American Academy of Pediatrics' recommendations and other current knowledge regarding ribavirin therapy.²⁸

IX. REFERENCES

1. Food and Drug Administration [1986]. Ribavirin aerosol approved for severe cases of RSV in infants and young children. FDA Drug Bulletin 16(1):7.
2. Smith R [1984]. Background and mechanisms of ribavirin action. In Smith R, Knight V, Smith J, eds. Clinical applications of ribavirin. Orlando, FL: Academic Press, pp 1-18.
3. Bell M, Hunter J, Mostafa S [1988]. Nebulized ribavirin for influenza B Viral pneumonia in a ventilated immunocompromised adult. Lancet 2:(1869) 1084-1085.
4. Murphy D, Rose C [1989]. Respiratory syncytial virus pneumonia in human immunodeficiency virus-infected man (letter). JAMA. 261:1147.
5. Smith C, Fox J [1980]. Double-blind evaluation of ribavirin in naturally occurring influenza. In Smith R, Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, pp 147-164.
6. Gilbert B, Wilson S, Knight V, et al. [1984]. Ribavirin small particle aerosol treatment of influenza in college students 1981-1983. In: Smith R, Knight V, Smith J, eds. Clinical applications of ribavirin. Orlando, FL: Academic Press, pp. 125-143.
7. ICN Pharmaceuticals, Inc. [1987]. Small particle aerosol generator model SPAG-2 6000 series instructions for use. Costa Mesa, California: ICN Pharmaceuticals, Inc. Operators Manual Part No. 9018.
8. Arnold S, Buchan R [1991]. Exposure to ribavirin aerosol. Appl Occup Environ Hyg. 6(4):271-279.
9. Kilham L, Ferm V [1977]. Congenital abnormalities induced in hamster embryos with ribavirin. Science 195:413-4.
10. Hillyard I [1980]. The preclinical toxicology and safety of ribavirin. In: Smith RA, Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, pp 59-71.
11. Ferm V, Willhite C, Kilham L [1978]. Teratogenic effects of ribavirin on hamster and rat embryos. Teratology 17:93-102.
12. Kochhar D, Penner J, Knudsen T [1980]. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Teratology and Applied Pharmacology 52:99-112.
13. Gallagher R, Givan N, Hazelden K, McGregor D, Ridgway P, de S. Wickramaratne G [March 1977]. Teratogenicity testing in baboons of virazole. Unpublished report from ICN Pharmaceuticals.

14. Marks M [1990]. Adverse drug reactions: United States experience II. *Pediatr Infect Dis J.* 9:(suppl):S117-S118.
15. American Hospital Formulary Service [1990]. AHFS Drug Information. Bethesda, MD: American Society of Hospital Pharmacists, Inc., pp 376-378.
16. Waskin H [1991]. Toxicology of antimicrobial aerosols: A review of aerosolized ribavirin and pentamidine. *Respir. Care* 36:1026-1036.
17. Janai H [1990]. Adverse drug reactions: United States experience. I. *Pediatr Infect Dis J.* 9:(Suppl):115S-116S.
19. Diamond S, Dupuis L [1989]. Contact lens damage due to ribavirin exposure (letter). *Drug Intell Clin Pharm.* 23:428-429.
20. Catlin D, Smith R, Samuels A [1980]. ¹⁴C-ribavirin: distribution and pharmacokinetics studies in rats, baboons, and man. In: Smith R, Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, 1980. pp 83-89.
21. California Department of Health Services [1988]. Health care worker exposure to ribavirin aerosol: field investigation FI-86-009. Berkeley, CA: California Department of Health Services, Occupational Health Surveillance and Evaluation Program.
22. EPA [1986]. Guidelines for the health assessment of suspected developmental toxicants. Washington DC: United States Environmental Protection Agency. *Federal Register* 51(185):34028-34040.
23. American Institute of Architects [1987]. Guidelines for Construction and Equipment of Hospital and Medical Facilities. Washington DC: The American Institute of Architects Press.
24. NIOSH [1984]. Ribavirin: Method 5027 (issued 5/15/89). In: Eller P, ed. NIOSH Manual of Analytical Methods, 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services. Public Health Service, Centers for Disease control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 84-100.
25. American National Standard Institute [1989]. American National Standard Commodity Specification for Air - Compressed Gas Association, Inc. Arlington, VA: Compressed Gas Association, Inc.
26. NIOSH [1987]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer. DHHS (NIOSH) Publication Number 87-108.

27. NIOSH [1987]. A NIOSH technical guide to industrial respiratory protection. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health, Division of Safety Research. DHHS (NIOSH) Publication No. 87-116.
28. American Academy of Pediatrics, Committee on Infectious Diseases [1987]. Ribavirin therapy of respiratory syncytial virus. Pediatrics. 79:475-478.

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1. Geisinger Wyoming Valley Medical Center
2. Employee representative
3. OSHA, Region III

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

Table 1
Full-Shift Personal Samples for Ribavirin
Geisinger Wyoming Valley Medical Center
Wilkes Barre, Pennsylvania
January 24, 1992
HETA 91-178

Job Title	Time in Room (minutes)	Sample Period (minutes)	Percent Time in Room	TWA Concentration ($\mu\text{g}/\text{m}^3$)
Nurse	25	368	6.7%	ND (5.4)
Nurse	5	366	1.3%	ND (5.5)

TWA: Time Weighted Average

$\mu\text{g}/\text{m}^3$: micrograms per cubic meter air

ND: Ribavirin was not detected. The laboratory limits of detection and quantitation were 2.0 and 4.2 μg per sample, respectively.

Values in () indicate the lowest detectable concentration, based on the limit of detection and the volume of air sampled.

Table 2
Short-Term Ribavirin Concentrations
Geisinger Wyoming Valley Medical Center
Wilkes Barre, Pennsylvania
January 24, 1992
HETA 91-178

Job Title	Sample Duration (minutes)	Lapel Sample Conc. ($\mu\text{g}/\text{m}^3$)	Inside-Hood Conc. ($\mu\text{g}/\text{m}^3$)
Nurse	12	670	ND (83)
Respiratory Therapist	12	125	ND (83)
Parent	81	185	ND (12)
Nurse	17	382	ND (59)

$\mu\text{g}/\text{m}^3$: micrograms per cubic meter air

ND: Ribavirin was not detected. The laboratory limits of detection and quantitation were 2.0 and 4.2 μg per sample, respectively.

Values in () indicate the lowest detectable concentration, based on the limit of detection and the volume of air sampled

Table 3
Area Samples for Ribavirin
Geisinger Wyoming Valley Medical Center
Wilkes Barre, Pennsylvania
January 24, 1992
HETA 91-178

Location	Sample Period	Sample Time (minutes)	Concentration ($\mu\text{g}/\text{m}^3$)
Inside curtain on cart next to bed	1920 - 0559	639	7.4 (1.6)
Inside curtain next to the SPAG	1920 - 0559	639	12.5 (1.6)
Outside curtain near entry point	1920 - 0554	634	ND (1.6)
Outside curtain on shelf about 4 feet from entry point	1920 - 0554	634	ND (1.6)
On shelf outside of treatment room	1930 - 0552	622	ND (1.6)
Nurses Station	1929 - 0550	621	ND (1.6)
Inside Care Cube	2000 - 2005	5	90,000
Inside Care Cube	2005 - 2010	5	88,000
Inside Care Cube	2155 - 2200	5	86,000

$\mu\text{g}/\text{m}^3$: micrograms per cubic meter air

ND: Ribavirin was non-detected. The laboratory limits of detection and quantitation were 2.0 and 4.2 μg per sample, respectively.

Values in () indicate the lowest detectable concentration, based on the limit of detection and the volume of air sampled.

90,000 $\mu\text{g}/\text{m}^3$ = 90 micrograms per liter ($\mu\text{g}/\text{L}$)

APPENDIX A

Because differences exist among the various classes of respirators with regard to their protective capabilities, respirators are assigned protection factors as guidance for their selection. A protection factor is the ratio of the concentration of a contaminant in the environment surrounding a respirator wearer to the concentration of the contaminant inside the respirator wearer's facepiece. The majority of assigned protection factors are based on quantitative fit factors rather than workplace protection factors. **Quantitative fit factors** are determined from tests in which a group of respirator wearers perform a specific regimen of head and body movements for a short period of time while in a laboratory test chamber containing a challenge aerosol. A **workplace protection factor** is a measure of the protection provided in a workplace under the actual conditions of that workplace by a properly functioning respirator which is correctly worn and used.¹ An **assigned protection factor** (APF) is the minimum expected workplace level of respiratory protection that would be provided by a properly functioning respirator, or class of respirators, to a stated percentage of properly fitted and trained users.² Table A-1 lists APFs for various classes of respirators.³ Most APFs are not based on measurements of actual field (workplace) performance; the majority of APFs are based solely on quantitative fit factors. To date, it should be noted that no relationship between quantitative fit test results and measured workplace performance testing has been established.³

The maximum use concentration for a respirator is generally determined by multiplying the assigned protection factor of a respirator by a contaminant's lowest occupational limit (i.e., Permissible Exposure Limit of the Occupational Safety and Health Administration, Recommended Exposure Limit of NIOSH, and Threshold Limit Value of the American Conference of Governmental Industrial Hygienist). Alternatively, the minimum level of protection necessary for a specific occupational application can be calculated after exposure estimates have been determined for environmental contaminants. This is usually done by dividing the highest 8-hour time-weighted average (TWA) exposure estimate of an airborne contaminant by the contaminant's lowest occupational exposure limit. Then a class of respiratory protection is selected with an assigned protection factor equal to or exceeding the required level of protection. For example, if a set of industrial hygiene samples collected during a particular operation produced 8-hour TWA exposure estimates ranging from 8 to 50 mg/m³ for a contaminant with an occupational exposure limit of 10 mg/m³, then a respirator with an assigned protection factor of at least 5 ($50/10 = 5$) would be selected. Such a respirator would reduce the highest exposure concentration to an in-mask concentration equal to, or less than, the contaminant's exposure limit for the majority of respiratory wearers.

TABLE A-1. --Assigned protection factor classification of respirators for protection against particulate exposures

(Adapted from *NIOSH Respirator Decision Logic* manual)

Assigned protection factor	Type of respirator
5	Single use or quarter mask ² respirator
10	Any air-purifying half-mask respirator including disposable ³ equipped with any type of particulate filter except single use ^{2,4} Any air-purifying full facepiece respirator equipped with any type of particulate filter ⁵ Any supplied-air respirator equipped with a half-mask and operated in a demand (negative pressure) mode ²
25	Any powered air-purifying respirator equipped with a hood or helmet and any type of particulate filter ⁴ Any supplied-air respirator equipped with a hood or helmet and operated in a continuous flow mode ⁴
50	Any air-purifying full facepiece respirator equipped with a high efficiency filter ² Any powered air-purifying respirator equipped with a tight-fitting facepiece and a high efficiency filter ⁴ Any supplied-air respirator equipped with a full facepiece and operated in a demand (negative pressure) mode ² Any supplied-air respirator equipped with a tight-fitting facepiece and operated in a continuous flow mode ⁴ Any self contained respirator equipped with a full facepiece and operated in a demand (negative pressure) mode ²
1,000	Any supplied-air respirator equipped with a half-mask and operated in a pressure demand or other positive pressure mode ²
2,000	Any supplied-air respirator equipped with a full facepiece and operated in a pressure demand or other positive pressure mode ²
10,000	Any self-contained respirator equipped with a full facepiece and operated in a pressure demand or other positive pressure mode ² Any supplied-air respirator equipped with a full facepiece operated in a pressure demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure demand or other positive pressure mode ²

- 1 Only high efficiency filters are permitted for protection against particulates having exposure limits less than 0.05 mg/m³.
- 2 The assigned protection factors (APF's) were determined by Los Alamos National Laboratories (LANL) by conducting quantitative fit testing on a panel of human volunteers [6].
- 3 An APF factor of 10 can be assigned to disposable particulate respirators if they have been properly fitted using a quantitative fit test.
- 4 APF's were based on a workplace protection factor (WPF) data or laboratory data more recently reported than the LANL data.
- 5 The APF was based on consideration of efficiency of dust, fume, and/or mist filters.

APPENDIX A REFERENCES

1. Myers WR, Lenhart SW, Campbell D, Provost G [1983]. Letter to the editor, Topic: respirator performance terminology. Am Ind hyg Assoc J 44:B25-26.
2. Guy HP [1985]. Respirator performance terminology. Am Ind Hyg Assoc J 46:B22 & B24.
3. NIOSH [1987]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer. DHHS (NIOSH) Publication Number 87-108.